Household Pesticides and Risk of Pediatric Brain Tumors

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A follow-up to a population-based case–control study of pediatric brain tumors in Los Angeles County, California, involving mothers of 224 cases and 218 controls, investigated the risk of household pesticide use from pregnancy to diagnosis. Risk was significantly elevated for prenatal exposure to flea/tick pesticides [odds ratio (OR) = 1.7; 95% confidence interval (CI), 1.1–2.6], particularly among subjects less than 5 years old at diagnosis (OR = 2.5; CI, 1.2–5.5). Prenatal risk was highest for mothers who prepared, applied, or cleaned up flea/tick products themselves (OR = 2.2; CI, 1.1–4.2; for subjects <5 years of age, OR = 5.4; CI, 1.3–22.3). A significant trend of increased risk with increased exposure was observed for number of pets treated (p = 0.04). Multivariate analysis of types of flea/tick products indicated that sprays/foggers were the only products significantly related to risk (OR = 10.8; CI, 1.3–89.1). Elevated risks were not observed for termite or lice treatments, pesticides for nuisance pests, or yard and garden insecticides, herbicides, fungicides, or snail killer. Certain precautions, if ignored, were associated with significant increased risk: evacuating the house after spraying or dusting for pests (OR = 1.6; CI, 1.0–2.6), delaying the harvest of food after pesticide treatment (OR = 3.6; CI, 1.0–13.7), and following instructions on pesticide labels (OR = 3.7; CI, 1.5–9.6). These findings indicate that chemicals used in flea/tick products may increase risk of pediatric brain tumors and suggest that further research be done to pinpoint specific chemicals involved. *Key words*: brain neoplasms, childhood neoplasms, environmental carcinogens, flea control, insecticides, pesticides. *Environ Health Perspect* 105:1214–1220 (1997). *http://ehis.niehs.nih.gov*

Pesticides have been suspected risk factors for brain tumors, but are difficult to study epidemiologically. In adults, populations most often studied are those exposed occupationally, such as farmers and other agricultural workers. These studies have not shown a conclusive relationship between pesticide exposure and brain tumor risk (1–9), possibly because of the difficulty in accurately estimating individual pesticide exposure. Many of these studies were based on job titles, with little or no data on specific chemical exposures. Agricultural occupations typically involve exposure not only to pesticides but also to several other potentially hazardous substances, such as dusts, solvents, fuels, and zoonotic agents (1). Cohort studies of pesticide applicators, despite a greater degree of job title specificity, have also reported inconsistent results (10–12).

Children are most likely to be exposed, either prenatally or directly, in the home. Several case–control studies have examined the use of household pesticides and risk of pediatric brain tumors, and results have been mixed (13–22). Only one of these, a population-based case–control study conducted in Missouri, was specifically designed to assess household pesticide exposure and thus collected detailed exposure data (16). Positive associations were observed for a variety of pesticides such as garden insecticides, pest strips, termite pesticides, and flea collars. Another case–control study of household pesticides reported pest strips as the most consistent pesticide related to a variety of childhood cancers, including brain cancer (23).

To our knowledge, few studies have attempted to assess other factors that may interact with pesticides to increase cancer risk. Of particular concern in relation to pediatric brain tumors is prenatal exposure to nitrosatable chemicals in pesticides; one class of N-nitroso compounds (NOC), nitrosoureas, causes brain tumors among offspring in several different species after transplacental exposure (24). However, an NOC precursor such as nitrite must first be present before nitrosation can occur. Therefore, nitrite exposure, such as through diet, may be an important modifier of risk of certain pesticides.

As a follow-up to our population-based case–control study of pediatric brain tumors diagnosed from 1984 through June 1991 in Los Angeles County, California, we reinterviewed 224 case and 218 control mothers to collect detailed data on their children's exposure to various pesticides, as well as parental farm occupation and precautions taken when using pesticides. Data on both prenatal and children's direct exposure were collected. This paper details our findings.

Methods

Subjects who participated in the Los Angeles County component of the U.S. West Coast childhood brain tumor study, a population-based case–control interview study (25), were eligible for the pesticide follow-up study. Briefly, cases eligible for the original West Coast study were diagnosed from 1984 through June 1991 in Los Angeles County, five counties in the San Francisco–Oakland Bay Area, and 13 counties in the Seattle–Puget Sound area with a primary tumor of the brain, cranial nerves, or cranial meninges (26) and were at most 19 years old at diagnosis. Additionally, we required that the biological mother be available for an interview in English or Spanish and that the household have a telephone. Controls were identified from random digit dialing (27) and matched to cases by gender and birth year. Each control was assigned as a reference date the date at which the control attained the age of the corresponding case at diagnosis. Five hundred forty cases and 801 controls were included in the original study. Of these, 304 cases and 315 controls were from Los Angeles County, which was 70 and 71% of all eligible Los Angeles County cases and controls, respectively (28). In-person interviews of case and control mothers were conducted from 1988 through 1992 and primarily emphasized prenatal and childhood exposure to NOC, such as from diet. Mothers were instructed to limit childhood exposures to those occurring before the date of diagnosis (cases) or reference date (controls), hereafter referred to as reference date for both cases and controls.

For the pesticide follow-up study, attempts were made to recontact all mothers from Los Angeles County who participated in the original study and for whom residence histories were available—all 304 cases and 304 of the controls. Seventy cases and 72 controls were nontraceable, 5 cases and 8 controls refused to participate, 1 case mother was deceased, and phone contact was unsuccessful for 4 cases and 6 controls. Thus, phone interviews were conducted from May 1994 through April 1995 with 224 case and 218 control mothers; this was 74% of case and 72% of control mothers

recontacted, or 51 and 49% of originally eligible cases and controls, respectively. Exposure data were collected on pesticides for termite control; pesticides for nuisance pests such as ants and roaches; lawn and garden insecticides, herbicides, fungicides, and snail baits; lice treatments; products for flea/tick control; parental farm occupations; and precautions taken when using pesticides. Several details of exposure were also

asked, including whether prenatal exposure occurred, child's age at first and last exposure, types and brand names of products used (Table 1), who prepared and cleaned up the product, duration of treatment, frequency of application of product, and duration of contact with treated areas. Mothers were again instructed to limit exposures to those occurring prior to the reference date. Residence histories, compiled for another

component of the Los Angeles County study (*28*), were used as recall aides. For example, the interviewer asked whether termite treatment occurred at each specific address of a subject's residence history.

Unconditional logistic regression was used to compute odds ratios (OR) and 95% confidence intervals (CI), adjusted for the matching variables (gender, age, birth year) (*29*). A priori hypotheses involving exposure to broad categories as well as specific types of pesticides were based on the case–control study of household pesticides and pediatric brain tumors done in Missouri. Separate analyses of prenatal exposures were done for subjects less than 5 years old at diagnosis because resulting carcinogenic effects are more likely to occur early in life. Analyses of precautions exercised when using pesticides was exploratory. The following variables were considered as possible confounders and/or modifiers of risk estimates: age (0–4 years, >4 years), birth year, race, mother's age, and socioeconomic status (SES), measured as a score representing both parents' occupations during the 5 years preceding the birth of the index child and their levels of education (*30*). An a priori hypothesis of interaction between NOC-containing pesticides and dietary nitrite was evaluated, based on prior knowledge of neurocarcinogenic effects of nitrosoureas and their precursors. Other variables evaluated for effect modification, primarily based on the NOC hypothesis, were mother's smoking status, medication use (fertility drugs, oral contraceptives, antiepileptics, analgesics, cold and cough remedies, drugs to prevent or induce miscarriage, diuretics, tranquilizers, antihistamines), and vitamin supplementation [both sidestream smoke and certain medications contain NOC; vitamins C and E are nitrosation inhibitors (*31*)]. Tumor-specific [astroglial tumor, primitive neuroectodermal tumor (PNET), other glial tumor] analyses were done using all controls as the comparison. Multiple logistic regression (*29*) was used to test for independent effects. Subjects with missing data were excluded from analyses involving those data. Reported *p*-values are two-sided.

Results

Social and demographic characteristics of the 224 cases and 218 controls who participated in the pesticide follow-up study and all 304 cases and 315 controls from the original study are shown in Table 2. In general, slightly more Los Angeles County cases than controls were non-Hispanic white, and cases tended to be of lower SES than controls. The pesticide study subgroup was largely representative of the original study group. Table 3 shows differences

Table 1. Specific brands, chemicals, product types, and pests targeted on the questionnaire for a case–control study of pesticide exposure and risk of pediatric brain tumor in Los Angeles County, California, 1984–1991

Type of pesticide	Brands or chemical names	Types of product or pest
Termite	Ortho-Klor Soil Insect and Termite Killer Chlordane Heptachlor Dursban T-C Purge Penta Copper napthenate Methylbromide gas Vikane Dragnet T-C Timbar T-C	Professional treatment[a] Nonprofessional treatment
Nuisance pest		Spray can Spray bottle or pump Dust or granules Bombs or fumigant Pest strip Ant stakes or trap Roach trap or bait
Lice	Kwell shampoo Kwell lotion or cream Nix cream rinse Scabene shampoo Scabene cream A-200 shampoo Eurax lotion or cream RID shampoo	
Lawn/garden	Sevin (carbaryl) Spectracide Ortho, nos Ortho Isotox Ortho Diazinon Ortho Flower or Vegetable Safer Soildrin Dexol Malathion Schultz Thiodan Weed-B-Gone (Spectracide) Roundup or Ortho-Kleenup Ortho Triox Preen Bug-geta, Last Bite, or Snarol Cooke's Ortho Funginex Daconil . Fore Lawn Fungicide Bravo	Aphids Whitefly Medflies Scales Mealy bugs Beetles Mites Worms or caterpillars Snails or slugs Mildew Leaf spot Rust Blight Weeds
Flea/tick		Spray Dust Shampoo or dip Bomb Carpet treatment

[a]Asked for all pesticides except lice products.

between case and control mothers in factors relevant to their pregnancies. As in the full West Coast study (540 cases, 801 controls), vitamin supplementation during pregnancy was significantly protective in this subgroup. On the other hand, the risk association with nitrite intake from cured meats during pregnancy seen in the full study (25) was not significant in this subgroup of the Los Angeles County study.

Analysis of both prenatal and childhood exposure to general categories of pesticides resulted in only one significant positive association, namely prenatal exposure to flea/tick products (Table 4). Risk estimates tended to be higher among higher SES subjects. All risk estimates for prenatal exposures were higher among mothers who took any kind of medication while pregnant (not shown), and risk associated with nuisance pest (e.g., ants, roaches) pesticides was significantly higher for mothers who took oral contraceptives (OR = 6.7; CI, 1.1–38.8). Among younger children (less than 5 years old at reference) with glial tumors other than astroglial or PNET, exposure to insecticides during childhood increased risk of brain tumor (OR = 3.8; CI, 1.0–14.6). The OR associated with childhood exposure to flea/tick products was 2.0 (CI, 1.0–4.0) among younger children; however, this was reduced to 1.3 (CI, 0.4–3.8) after adjustment for prenatal exposure.

Table 5 presents a detailed analysis of prenatal flea/tick product exposure, both for all subjects and for subjects less than 5 years old at the reference date. Risk estimates were adjusted for race (non-Hispanic white vs. all other ethnicities) and vitamin supplementation. Adjustment for race was used rather than SES because in the original study group, race was more strongly correlated with pet ownership (measured by cat ownership—the only pet data available in the original study) than was SES; 27% of all Los Angeles County non-Hispanic whites in the original study owned cats compared to 11% of all other ethnicities. Because use of flea/tick products is highly dependent on pet ownership and cases were more likely than controls to be non-Hispanic white, we felt this adjustment was appropriate, despite the possibility of overmatching (which biases towards the null). Univariate ORs (CIs) for individual product types were 2.8 (0.9–8.1) for sprays, 5.6 (0.6–49.8) for foggers, 1.2 (0.4–3.5) for dusts/powders, 1.5 (0.9–2.5) for shampoos, and 1.5 (0.9–2.5) for collars. For subjects less than 5 years old at diagnosis, ORs (CIs) were 3.0 (0.7–13.1) for sprays, 3.9 (0.4–38.3) for foggers, 0.9 (0.1–7.0) for dusts/powders, 2.2 (0.9–5.4) for shampoos, and 2.0 (1.0–4.3) for collars. In a multivariate analysis of type of flea/tick

Table 2. Characteristics of participants in a case–control study of pediatric brain tumor in Los Angeles County, California 1984–1991

Characteristic	Pesticide study		Original study	
	No. cases (%)	No. controls (%)	No. cases (%)	No. controls (%)
Sex				
Male	122 (54)	121 (56)	165 (54)	173 (55)
Female	102 (46)	97 (45)	139 (46)	142 (45)
Age (years)				
≤4	73 (33)	73 (33)	105 (35)	113 (36)
5–9	68 (30)	57 (26)	88 (29)	88 (28)
10–19	83 (37)	88 (40)	111 (37)	114 (36)
Birth year				
1965–1975	66 (29)	68 (31)	85 (28)	86 (27)
1976–1980	51 (23)	47 (22)	68 (22)	72 (23)
1981–1985	71 (32)	64 (29)	98 (32)	93 (30)
1986–1990	36 (16)	39 (18)	53 (17)	64 (20)
Race/ethnicity				
Non-Hispanic white	93 (42)	80 (37)	112 (37)	101 (32)
Hispanic	96 (43)	103 (47)	139 (46)	165 (53)
African American	16 (7)	17 (8)	28 (9)	27 (9)
Asian	12 (5)	13 (6)	16 (5)	16 (5)
Other	7 (3)	5 (2)	9 (3)	5 (2)
Socioeconomic status[a]				
Lower	134 (60)	126 (58)	199 (65)	200 (64)
Higher	90 (40)	92 (42)	105 (35)	114 (36)
Tumor type				
Astroglial	112 (50)		155 (51)	
Medulloblastoma/primitive neuroectodermal	47 (21)		66 (22)	
Other	65 (29)		83 (27)	

[a]Based on parents' education and occupation according to the Hollingshead Social Index (27): Lower, ≥40; Higher, <40.

Table 3. Characteristics of mothers during pregnancy in a case–control study of pesticide exposure and risk of pediatric brain tumor in Los Angeles County, California, 1984–1991

Characteristic	No. cases (%)	No. controls (%)	OR (CI)
Age (years)			
15–24	82 (37)	80 (37)	1.0
25–29	76 (34)	76 (35)	1.0 (0.6–1.5)
30–44	66 (29)	62 (28)	1.1 (0.7–1.7)
Smoked cigarettes			
No	192 (86)	189 (87)	1.0
Yes	32 (14)	29 (13)	1.1 (0.6–1.9)
Took medication			
No	142 (63)	144 (66)	1.0
Yes	82 (37)	74 (34)	1.2 (0.8–1.8)
Took vitamins			
No	46 (21)	22 (10)	1.0
Yes	174 (79)	189 (90)	0.4 (0.2–0.8)
Nitrite intake from cured meats[a]			
Low	101 (48)	112 (52)	1.0
High	109 (52)	104 (48)	1.2 (0.8–1.7)

Abbreviations: OR, odds ratio; CI, 95% confidence interval.
[a]Low, <0.15 average daily milligrams; high, ≥0.15 average daily milligrams.

product, only sprays/foggers were significantly related to risk, although the multivariate approach suffered from sparse numbers. Sprays and foggers were combined to achieve convergence [univariate ORs were similar and exposures were independent: 18 mothers (13 case, 5 control) used sprays, 6 mothers (5 case, 1 control) used foggers, 1 mother (case) used both sprays and foggers]. Stratification by nitrite intake from cured

meats resulted in an appreciable change in risk only for powders/dusts: 5 of 7 case mothers and 0 of 9 control mothers exposed to powders/dusts had higher than average (≥ 0.15 daily mg) exposure to nitrite from cured meats during pregnancy. Risk was higher when the mother was directly involved in product preparation, application, and clean-up. Two of three measures of dose response [number of pets treated,

Table 4. Prenatal and childhood exposure to general categories of pesticides in a case–control study of pesticide exposure and risk of pediatric brain tumor in Los Angeles County, California, 1984–1991

Type of pesticide	Prenatal exposure			Childhood exposure		
	No. cases (%)	No. controls (%)	OR (CI)	No. cases (%)	No. controls (%)	OR (CI)
Termite	5 (2)	2 (1)	2.7 (0.5–14.2)	23 (11)	32 (15)	0.7 (0.4–1.3)
Nuisance pest	106 (50)	97 (47)	1.1 (0.8–1.7)	150 (68)	146 (69)	1.0 (0.6–1.5)
Lice	2 (1)	0 (0)	–	38 (17)	50 (23)	0.6 (0.4–1.0)
Insecticides	26 (12)	20 (10)	1.3 (0.7–2.4)	57 (28)	47 (24)	1.2 (0.8–2.0)
Herbicides	2 (1)	3 (1)	0.9 (0.1–6.1)	4 (2)	4 (2)	1.2 (0.3–4.9)
Fungicides	0 (0)	2 (1)	–	1 (1)	8 (4)	0.1 (0.0–1.0)
Snail killer	21 (10)	18 (9)	1.1 (0.6–2.1)	41 (21)	38 (20)	1.0 (0.6–1.8)
Flea/tick	76 (34)	53 (25)	1.7 (1.1–2.6)	106 (47)	102 (47)	1.0 (0.7–1.4)

Abbreviations: OR, odds ratio; CI, 95% confidence interval.

Table 5. Prenatal exposure to flea/tick products in a case–control study of pesticide exposure and risk of pediatric brain tumor in Los Angeles County, California, 1984–1991

	All subjects			Subjects aged 0–4 years		
	No. cases (%)	No. controls (%)	OR (CI)[a]	No. cases (%)	No. controls (%)	OR (CI)[a]
Exposed	75 (34)	52 (25)	1.7 (1.1–2.6)	29 (40)	18 (25)	2.5 (1.2–5.5)
Type of product used (multivariate)[b]						
Spray/fogger	17 (8)	6 (3)	10.8 (1.3–89.1)	7 (10)	1 (1)	6.6 (0.7–62.7)
Powder/dust	9 (5)	7 (4)	0.9 (0.2–3.6)	2 (1)	1 (1)	–
Shampoo/dip	47 (23)	33 (17)	1.2 (0.6–2.5)	16 (24)	11 (15)	1.9 (0.7–5.4)
Collar	54 (25)	39 (19)	1.1 (0.5–2.1)	19 (28)	14 (19)	1.3 (0.5–3.4)
Product prepared/cleaned up by						
Mother	33 (17)	17 (9)	2.2 (1.1–4.2)	10 (16)	3 (5)	5.4 (1.3–22.3)
Other	34 (17)	26 (13)	1.4 (0.8–2.5)	17 (25)	10 (14)	2.3 (0.9–5.9)
No. pets for which products were used[c]						
1	43 (20)	35 (17)	1.4 (0.9–2.4)	16 (23)	13 (18)	2.0 (0.8–4.8)
>1	30 (14)	17 (8)	2.0 (1.0–4.0)	11 (16)	5 (7)	3.5 (1.1–11.4)
Average hr/day spent with pet treated with flea/tick products[d]						
≤3	33 (15)	33 (15)	1.1 (0.6–1.8)	10 (15)	10 (14)	1.3 (0.5–3.6)
>3	21 (10)	12 (6)	1.9 (0.9–4.2)	8 (12)	4 (5)	3.2 (0.8–12.2)
Average frequency of application						
Once to every other month	30 (14)	17 (8)	1.9 (1.0–3.8)	12 (17)	4 (6)	4.4 (1.2–15.5)
>Every other month	26 (12)	22 (10)	1.3 (0.7–2.4)	8 (11)	7 (10)	1.9 (0.6–6.0)

Abbreviations: OR, odds ratio; CI, 95% confidence interval.
[a]Adjusted for race (white vs. non-white) and maternal vitamin supplementation during pregnancy; subjects with missing vitamin data (4 cases, 7 controls) were excluded from analysis.
[b]For subjects aged 0–4 years, dusts/powders were excluded from analysis to achieve convergence.
[c]p-trend = 0.04 for all subjects and for subjects aged 0–4 years.
[d]p-trend = 0.08 for all subjects and 0.07 for subjects aged 0–4 years.

time spent with treated pet(s)] indicated increasing risk with increasing exposure. Age of the child at tumor diagnosis and maternal nitrite intake from cured meats appeared to be the only effect modifiers.

Very few parents worked on a farm, and there was no increased risk among offspring of those who did. Restricting analysis to professional pesticide treatment had no effect on risk for any of the pesticide categories, nor did restricting exposure to indoor treatment. Although risk from prenatal exposure to termite treatment was elevated (OR = 2.7), only seven subjects (5 cases, 2 controls) were exposed (CI, 0.5–14.2). Mothers were generally unable to recall specific chemicals that were used. Only four mothers (3 cases, 1 control) reported use of chlordane (for termite treatment), and only four mothers (all control) reported use of DDT (for nuisance pests).

For pesticides other than flea/tick products, no consistent risk associations were observed for any particular product type, such as pest strips, or any brand name.

Table 6 describes several precautions associated with pesticide use and reports risk by how often precautions were exercised. These questions were not asked for each exposure period (prenatal, childhood), but rather for use of pesticides by anyone in the household at any time. Risk was significantly increased for those who reported that 1) family members never evacuated the house after spraying or dusting for pests, 2) harvest of food was not always delayed for the recommended period of time after pesticide treatment, and 3) pesticide label instructions were never followed. None of the precautions was associated with a significant trend [using response category (e.g., always, usually, sometimes, never) as a continuous variable] of increasing

risk with decreasing frequency of using the precaution.

Discussion

Most epidemiological research done to date on pesticides and pediatric brain tumor risk has focused on nonspecific pesticide use, and findings from these studies have been inconclusive. Some investigators have noted increased risk of brain tumor among children generally exposed to pesticides (13,17), but several studies, including ours, have not supported this observation (14,15,17,20,23). Increased risk has more often been reported for general pesticide exposure to the mother during pregnancy (14,18,19,22), but, again, not consistently (21). Only the Missouri study, on which our a priori hypotheses were based, collected data as detailed as ours (16). Several pesticide exposures during childhood were associated with increased

risk, including general pesticides for nuisance pests, pest strips, termite treatment, lice treatment, garden and orchard insecticides (specifically carbaryl and diazinon), and herbicides. We found no risk increases for any of these exposures during childhood. However, exposure prevalences of pest strips, herbicides, and carbaryl or diazinon as garden insecticides were nonexistent or very low; thus, risk of these exposures could not be effectively evaluated. Among prenatal exposures, the Missouri study (16) observed elevated risks for nuisance pest foggers and pest strips. No mothers in our study reported use of pest strips during pregnancy, and no increase in risk was observed for use of nuisance pest (e.g., ants, roaches) foggers during pregnancy.

The only exposure we studied that produced a significantly increased risk of pediatric brain tumor was prenatal exposure to flea/tick products, especially among children diagnosed at younger ages (less than 5 years). Risk appeared to be primarily confined to sprays/foggers rather than shampoos/dips, powders/dusts, and collars. This finding directly contrasts with the Missouri study (16) in which collars but not sprays significantly increased risk. Further, risk was not elevated for prenatal exposure to any flea/tick product in the Missouri study, which found elevated pet-associated risk estimates only for childhood exposure to pet pesticides together with direct exposure to the pet. We found no increased risk for this composite exposure. The Missouri study authors, it should be noted, acknowledged that a small sample size (45 cases) precluded meaningful analyses, particularly of specific pet pesticides (16).

Using the EPA Office of Pesticide Programs (OPP) database of all pesticides ever registered in California (32), we tabulated the most common pesticides found in shampoos, dips, sprays, powders, dusts, foggers, and collars registered between 1965 and 1990, the range of birth years among our subjects (Table 7). The OPP database was searched by product name, and only those products with the word "flea" or "fleas" were retrieved. Also, only products whose names identified the category of product to which it belonged (e.g., shampoo) were included (738/931).

Pyrethrins and pyrethroids (synthetic pyrethrins such as permethrin, tetramethrin, allethrin, resmethrin, and fenvalerate) were common to all flea/tick products except collars, but were most prevalent in shampoos (primarily pyrethrins). This group of pesticides is commonly used in household pest products to provide a quick kill. Pyrethrins are considered very safe for both humans and pets because they are

Table 6. Precautions taken before and after pesticide use in a case–control study of pesticide exposure and risk of pediatric brain tumor in Los Angeles County, California, 1984–1991

Precaution	No. cases (%)	No. controls (%)	OR (CI)[a]
House evacuated when spraying/dusting			
Always	71 (32)	69 (32)	1.3 (0.8–2.1)
Usually/sometimes	10 (4)	12 (6)	1.0 (0.4–2.6)
Never	80 (36)	62 (28)	1.6 (1.0–2.6)
Utensils covered while spraying/dusting			
Always	120 (54)	102 (47)	1.5 (1.0–2.3)
Usually/sometimes	8 (4)	7 (3)	1.7 (0.6–4.9)
Never	24 (11)	21 (10)	1.5 (0.7–2.9)
Harvest of food delayed after treatment			
Always	16 (7)	15 (7)	1.2 (0.6–2.5)
Not always	10 (5)	3 (1)	3.6 (1.0–13.7)
Foods washed before eating			
Always	32 (14)	22 (10)	1.5 (0.8–2.8)
Not always	5 (2)	3 (1)	1.8 (0.4–7.7)
Avoid handling pets after flea/tick treatment			
Always	17 (8)	16 (7)	0.9 (0.4–1.9)
Usually/sometimes	5 (2)	5 (2)	0.8 (0.2–3.1)
Never	63 (29)	71 (33)	0.8 (0.5–1.3)
Person that applied pesticides wore gloves			
Always	37 (17)	41 (19)	0.9 (0.5–1.7)
Usually/sometimes	6 (3)	11 (5)	0.5 (0.2–1.7)
Never	136 (62)	121 (57)	1.1 (0.7–1.9)
Person that applied pesticides washed immediately			
Always	149 (70)	152 (73)	1.0 (0.6–1.6)
Usually/sometimes	8 (4)	6 (3)	1.5 (0.5–4.9)
Never	17 (8)	10 (5)	1.7 (0.7–4.4)
Pesticides stored out of reach of children			
Always	175 (78)	166 (77)	1.1 (0.7–1.9)
Not always	7 (3)	7 (3)	1.2 (0.4–3.9)
Followed label instructions			
Completely, every time	71 (32)	68 (32)	1.2 (0.7–2.1)
Usually/occasionally	40 (18)	35 (16)	1.3 (0.7–2.6)
First time, seldom again	47 (21)	62 (29)	0.8 (0.5–1.5)
Never	24 (11)	8 (4)	3.7 (1.5–9.6)

Abbreviations: OR, odds ratio; CI, 95% confidence interval.
[a]For each precaution, the reference group is subjects who responded that they did not use the pesticide in question.

natural plant extracts that are easily metabolized (33). In products other than shampoos, pyrethrins and pyrethroids are usually combined with other pesticides that can provide a residual effect (up to 30 days), usually carbamates or organophosphates. Carbamates and organophosphates inhibit acetylcholinesterase in the nervous system, resulting in toxic levels of the neurotransmitter acetylcholine. Chlorpyrifos, an organophosphate, was relatively common only in sprays. Repeated low-dose exposure to chlorpyrifos has been shown to cause extensive neurochemical and neurobehavioral changes in gestating rats (34). Because of findings from the EPA reregistration review process that chlorpyrifos has been associated with neurotoxic effects in humans, DowElanco, the manufacturer of chlorpyrifos, has recently agreed to restrict its recommended uses, including the elimination of indoor use for fleas/ticks and in direct pet applications (35). Carbaryl (a carbamate) was a possible ingredient of all

products except shampoos and dips, but was most frequently used in powders (65% of all powder products) and dusts (85% of all dust products). The EPA has classified carbaryl as noncarcinogenic; however, carbaryl reacts with nitrite at pH 1, which can be reached in the human stomach, and the most important source of high nitrite concentration in the stomach is likely to be cured meats (25,31). The product of carbaryl nitrosation is nitrosocarbaryl, a proven skin and forestomach carcinogen in mice (36–39). In our study, among mothers who used flea/tick powders or dusts during pregnancy, case mothers were more likely than control mothers to have had higher than average nitrite intake from cured meats (5/7 case vs. 0/9 control).

Among younger children in our study, the decrease in risk for exposure to flea/tick pesticides during childhood after adjustment for prenatal exposure is noteworthy, suggesting that the fetal brain may be especially vulnerable to potentially carcinogenic

Table 7. Most common pesticides in flea/tick products registered with the California Office of Pesticide Programs[a] before 1990[b]

Type of product	No. registered	Most common chemicals	No. products (%)
Shampoo	111	Pyrethrins	87 (78)
		Aliphatic petroleum hydrocarbons	23 (21)
Dip	54	Pyrethrins	26 (48)
		Aliphatic petroleum hydrocarbons	7 (13)
		Permethrin	7 (13)
		Malathion	6 (11)
		Rotenone	6 (11)
Spray	309	Pyrethrins	198 (64)
		Aliphatic petroleum hydrocarbons	71 (23)
		Chlorpyrifos	43 (14)
		Carbaryl	42 (14)
		Permethrin	36 (12)
Powder	120	Carbaryl	78 (65)
		Pyrethrins	41 (34)
		Silica gel	19 (16)
		Dichlorophene	14 (12)
Dust	13	Carbaryl	11 (85)
		Pyrethrins	3 (23)
		Silica gel	3 (23)
Fogger	17	Pyrethrins	7 (41)
		Aliphatic petroleum hydrocarbons	5 (29)
		Fenvalerate	5 (29)
		Tetramethrin	5 (29)
		Malathion	3 (18)
		Allethrin	2 (12)
		Carbaryl	2 (12)
		Permethrin	2 (12)
		Resmethrin	2 (12)
Collar	65	Dichlorvos	18 (28)
		Lindane	13 (20)
		Propoxur	8 (7)
		Carbaryl	7 (11)

[a]Data from California EPA Department of Pesticide Regulation (*32*).
[b]Includes only shampoos, dips, sprays, powders, dusts, foggers, and collars for which the product name identifies the category of product to which it belongs (738/931).

effects of pesticides. One group of NOC, nitrosoureas, are proven nervous system carcinogens (*40,41*) and are highly effective when exposure is transplacental; relatively low levels of nitrosourea precursors (sodium nitrite and ethylurea) in the food and drinking water of pregnant rats can cause a high incidence of tumor induction in offspring (*24*).

Most chemicals used in flea/tick products are common to several different types of household pesticides. Thus, the lack of an increased risk in our study with use of other types of pesticides, such as sprays and dusts for nuisance pests, appears to conflict with the flea/tick product finding. Differential recall of flea/tick products, which may be exacerbated by a second interview, is a possible explanation. For example, risk estimates for prenatal exposures were generally higher among mothers who reported medication use during pregnancy, which may indicate a tendency for case mothers to report more exposures. Case mothers may have been more likely to report flea/tick product exposure given that childhood cancer was linked

to certain flea/tick products during the mid-1980s in media coverage of a National Toxicology Program study (*42*). However, the product primarily targeted was dichlorvos in flea/tick collars for which risk was not elevated in our study. Also, risk estimates were not elevated for childhood exposure to flea/tick products. We used several techniques to minimize recall bias. While it was not possible to blind interviewers as to disease status of the subjects, all interviewers used the same structured questionnaire for both cases and controls, consisting of a fixed script that included introductory and transitional statements. Explicit instructions were provided as to how and when to use recall probes to ensure that probing was independent of disease status. Another explanation for the null risk association for non-flea/tick pesticides is that risk estimates for exposures that are difficult to recall are biased towards the null, and it may be argued that use of flea/tick products is easier to remember (because it is usually referenced by a particular pet) than pesticide use for nuisance pests. Household pesticide use in general is a very

common exposure [85% of U.S. households (*42*)], with many different products commercially available. Detailed data on both types and brands (ingredient content differs widely by brand) of pesticides used in the past are important so that specific chemicals can be pinpointed, but these are not easily recalled. Also, only mothers were interviewed, and data on certain types of pesticide applications, such as house exterminations and yard treatments, may be better ascertained from fathers in two-parent families.

The reliance on recall is an obvious limitation of retrospective data. The relatively low 50% participation rate for our study is also a serious concern. In general, the subset of subjects included was representative of the original study participants. Subjects in the pesticide study had somewhat higher SES than the original group; however, this was true of both cases and controls. Since we have no data to characterize the eligible cases and controls that did not participate in the original study, selection bias cannot be ruled out as a possible factor in our results.

Despite the lack of exposure specificity of retrospective studies done to date, there appears to be enough evidence to warrant further investigation of pesticide use during pregnancy and health effects in offspring in the first few years of life. We observed a significant increased brain tumor risk only for flea/tick products, suggesting that, in general, case mothers were not more likely than control mothers to report pesticide use. Further, use of household pesticides other than flea/tick products (many of which contain the same chemicals as flea/tick products) may be more difficult to recall, in which case risk associations with those products would be masked (due to nondifferential measurement error). Therefore, there is a need for additional research into potential cancer risks of specific chemicals used in household pesticides, but particularly those used in flea/tick sprays and foggers because, in our study, risk was specific to those products. Also, our findings suggest that interaction between carbaryl, commonly found in flea/tick powders/dusts but also used in other household pesticides, and nitrite may be an important consideration in determining cancer risk.

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